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(54) Title: COMPOSITION COMPRISING A PDE-4 INHIBITOR AND H1-RECEPTOR ANTAGONIST AND THE USE THEREOF FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF RESPIRATORY DISEASES

(57) Abstract: This invention relates to treating pulmonary diseases such as chronic obstructive pulmonary disease or asthma by administering a phosphodiesterase 4 inhibitor in combination with an H_1 -receptor antagonist.

COMPOSITION COMPRISING A PDE-4 INHIBITOR AND A H1-RECEPTOR ANTAGONIST AND THE USE THEREOF FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF RESPIRATORY DISEASES

Area of the Invention

This invention relates compositions and methods for preventing or reducing the onset of symptoms of pulmonary diseases, or treating or reducing the severity of pulmonary diseases. In particular it relates to compositions and methods for treating pulmonary diseases by administering a PDE 4 inhibitor and an H_1-receptor antagonist.

Background of the Invention

Identification of novel therapeutic agents for treating pulmonary diseases is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator could have a substantial effect on all other components of a particular pulmonary disease. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease. The approach as set forth in this invention utilizes two the combination of such a regulator, a PDE4-specific inhibitor with an H_1-receptor antagonist.

PDE4-specific inhibitors represent a new approach to cell regulation by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts Mg^{+2}-ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma and rhinitis. As such, an elevation of cAMP should produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE 4, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE 4 inhibitors

are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case *in vivo*. Thus PDE 4 inhibitors, and particularly PDE4-specific inhibitors, would be effective in the respiratory tract, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated.

In addition, it could be useful to combine therapies, in light of the fact that the etiology of many pulmonary diseases involves multiple mediators. In this invention there is presented the combination of a PDE 4 inhibitor and an H_1-receptor antagonist, often called simply an antihistamine, for treating pulmonary diseases, particularly chronic obstructive pulmonary disease (COPD), asthma or a related pulmonary disease such as chronic bronchitis or allergic rhinitis. To the extent that a respiratory disease is distinct from a pulmonary disease, the former is within the scope of this invention as well.

Summary of the Invention

In a first aspect this invention relates to a method of prophylaxis of, treating, or reducing the exacerbations associated with, a respiratory or pulmonary disease by administering to a patient in need thereof an effective amount of a PDE 4 inhibitor and an H_1-receptor antagonist either in a single combined form, separately, or separately and sequentially where the sequential administration is close in time, or remote in time.

In a second aspect this invention relates to a composition for the prophylaxis of, treating, or reducing the exacerbations associated with, a respiratory or pulmonary disease comprising an effective amount of a PDE4 inhibitor, an effective amount of an H_1-receptor antagonist and a pharmaceutically acceptable excipient.

In a third aspect this invention relates to a method for preparing a composition which is effective for the prophylaxis of, treating, or reducing the exacerbations associated with, a respiratory or pulmonary disease which method comprises mixing an effective amount of a PDE4 inhibitor and an H_1-receptor antagonist with a pharmaceutically acceptable excipient.

In a fourth aspect there is provided use of an effective amount of a PDE 4 inhibitor and an H_1-receptor antagonist either in a single combined form, separately, or separately and sequentially where the sequential administration is close in time, or remote in time in the manufacture of a medicament or medicament pack for the prophylaxis of, treating, or reducing the exacerbations associated with, a respiratory or pulmonary disease.

In a fifth aspect there is provided use of a composition comprising an effective amount of a PDE4 inhibitor, an effective amount of an H_1-receptor antagonist and a pharmaceutically acceptable excipient in the manufacture of a medicament for the prophylaxis of, treating, or reducing the exacerbations associated with, a respiratory or pulmonary disease.

Detailed Description of the Invention

The combination therapy contemplated by this invention comprises administering a PDE4 inhibitor or a PDE3/4 mixed inhibitor with an H_1-receptor antagonist to prevent onset of

a respiratory or pulmonary disease event, to treat an existing condition, or to reduce the frequency or severity of exacerbations often occurring in patients suffering from a seasonal, episodic, or chronic respiratory or pulmonary disease. The compounds may be administered together in a single dosage form. Or they may be administered in different dosage forms. They may be administered at the same time. Or they may be administered either close in time or remotely, such as where one drug is administered in the morning or the second drug is administered in the evening. The combination may be used prophylactically or after the onset of symptoms has occurred. In some instances the combination(s) may be used to prevent the progression of a disease or to arrest the decline of a function, such as lung function. In addition, this combination is useful for reducing the incidences and/or severity of exacerbations of some pulmonary diseases, such as COPD. See co-pending U.S. provisional application 60/221,275 filed 27 July 2000 for test methods for determining and evaluating the affects of this combination on the frequency and severity of exacerbations in COPD patients. That methodology, and the full disclosure of that application, is incorporated herein in full as if set forth herein.

The PDE4 inhibitor useful in this invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act in as PDE4 inhibitor, and which is only or essentially only a PDE4 inhibitor, not compounds which inhibit to a degree of exhibiting a therapeutic effect other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 antagonists which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE 4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

PDE inhibitors used in treating inflammation and as bronchodilators, drugs like theophylline and pentoxyfyllin, inhibit PDE isozymes indiscriminently in all tissues. These compounds exhibit side effects, apparently because they non-selectively inhibit all 5 PDE isozyme classes in all tissues. The targeted disease state may be effectively treated by such compounds, but unwanted secondary effects may be exhibited which, if they could be avoided or minimized, would increase the overall therapeutic effect of this approach to treating certain disease states. For example, clinical studies with the selective PDE 4 inhibitor rolipram, which was being developed as an antidepressant, indicate it has psychotropic activity and produces gastrointestinal effects, e.g., pyrosis, nausea and emesis.

It turns out that there are at least two binding forms on human monocyte recombinant PDE 4 (hPDE 4) at which inhibitors bind. One explanation for these observations is that hPDE 4 exists in two distinct forms. One binds the likes of rolipram and denbufylline with a high affinity while the other binds these compounds with a low affinity. The preferred PDE4 inhibitors of for use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where

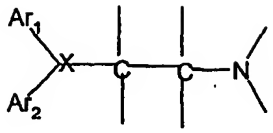
the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE 4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

Reference is made to U.S. patent 5,998,428, which describes these methods in more detail. It is incorporated herein in full as though set forth herein.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0.

Preferred compounds are *cis* [cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate] also known as cilomilast or Ariflo ®, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, and *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. They can be made by the processed described in US patents 5,449,686 and 5,552,438. Other PDE4 inhibitors, specific inhibitors, which can be used in this invention are AWD-12-281 [N-(3,5-dichloropyrid-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide)] from Astra (Hofgen, N. *et al.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787; Parke-Davis/Warner-Lambert); a benzodioxole derivative Kyowa Hakko disclosed in WO 9916766; V-11294A from Napp (Landells, L.J. *et al.* Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12(Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO 9947505) from Byk-Gulden; or a compound identified as T-440 (Tanabe Seiyaku; Fuji, K. et al. *J Pharmacol Exp Ther*,1998, 284(1): 162). Also, the PDE4 inhibitors identified in the literature as Bayer 19-8004, Zambon's compound Z15370A and Asta Medica's AWD 12-281 and AWD 12-343 can be used in this invention. Any one or all of these compounds may or could benefit from the process described herein.

The H_1-receptor antagonists, commonly called "antihistamines", may be any one or more of the numerous antagonists developed since Bovet and Staub first identified histamine-blocking activity using a phenolic ether in 1937. Much research followed, and currently there are many compounds known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

These compounds are available through commercial sources. In addition, they are described in some detail in the text Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Ed, 1996, McGraw-Hill at pages 586 to 591 and more fully in The Physicians Desk Reference, (Vol. 54, 2000, Medical Economic Co., Montvale, NJ, USA. Both references provide information about each compound, dosing and routes of administration, with exemplary formulation data.

One or more of these antihistamines can be use with one or more PDE4 inhibitors for prophylaxis or treatment.

A preferred combination therapy is that of loratadine and cilomilast or roflumilast.

All compounds mentioned may, if desired and appropriate, be employed in the form of alternative pharmaceutically acceptable derivatives, eg. salts and esters thereof.

These drugs are usually administered as an oral preparation or a nasal spray or aerosol, or as an inhaled powder. This invention contemplates either co-administering both drugs in one delivery form such as an inhaler, that is, putting both drugs in the same inhaler.

Alternatively one can put the PDE4 inhibitor into pills and package them with an inhaler that contains the antihistamine, or vica versa.

The present compounds and pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules, controlled-release preparation or lozenges or as an inhalable preparation.

A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical compositions for inhalation are in the form of a dry powder, solution, suspension or emulsion. Administration may for example be by dry powder inhaler (such as unit dose or multi-dose inhaler, e.g. as described in US Patent 5590645 or by nebulisation or in the form of a pressurized aerosol. Dry powder compositions typically employ a carrier such as lactose, trehalose or starch. Compositions for nebulisation typically employ water as vehicle. Pressurized aerosols typically employ a propellant such as dichlorodifluoromethane, trichlorofluoromethane or, more preferably, 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof. Pressurized aerosol formulations may be in the form of a solution (perhaps employing a solubilising agent such as ethanol) or a suspension which may be excipient free or employ excipients including surfactants and/or co-solvents (e.g. ethanol). In dry powder compositions and suspension aerosol compositions the active ingredient will preferably be of a size suitable for inhalation (typically having mass median diameter (MMD) less than 20 microns e.g. 1-10 especially 1-5 microns). Size reduction of the active ingredient may be necessary e.g. by micronisation.

Pressurized aerosol compositions will generally be filled into canisters fitted with a valve, especially a metering valve. Canisters may optionally be coated with a plastics material e.g. a fluorocarbon polymer as described in WO96/32150. Canisters will be fitted into an actuator adapted for buccal delivery.

Typical compositions for nasal delivery include those mentioned above for inhalation and further include non-pressurized compositions in the form of a solution or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as

buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents which may be administered by nasal pump.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.3 mg to 60 mg/Kg, and preferably from 1 mg to 30 mg/Kg of a compound or a pharmaceutically acceptable salt thereof. Preferred doses include 1 mg and 60 mg/Kg for treating COPD. Each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of the compound or a pharmaceutically acceptable salt thereof. Each dosage unit for intranasal administration contains suitably 1-400 mcg and preferably 10 to 200 mcg per activation. A dry powder inhalation dose could contain 1 - 1000 micrograms per dose unit. A topical formulation contains suitably 0.001 to 5.0% of a present compound.

The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity. Preferably, the active ingredient is administered once or twice a day.

It is contemplated that both active agents would be administered at the same time, or very close in time. Alternatively, one drug could be taken in the morning and one later in the day. Or in another scenario, one drug could be taken twice daily and the other once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably both drugs would be taken together at the same time and be administered as an admixture.

The following examples are provided to illustrate how to make and use the invention. They are not in any way intended to limit the scope of the invention in any manner or to any degree. Please refer to the claims for what is reserved to the inventors hereunder.

Examples

The following eight assays spread among five species were used to develop data supporting the selection of an IC_{50} ratio of about 0.1 or greater. The assays were: stimulation of acid production from rabbit isolated parietal gland; inhibition of FMLP-induced degranulation (release of myeloperoxidase) in human neutrophils; inhibition of FMLP-included O_2^- formation in guinea pig eosinophils; inhibition of LPS-induced TNF_α production in human monocytes; production of emesis in dogs; inhibition of antigen-induced bronchoconstriction in guinea pigs; reversal of reserpine-induced hypothermia in mice; and inhibition of LPS-induced TNF_α production from adoptively-transferred human monocytes in mice. These assays and data are presented below.

Statistical Analysis

To examine the hypothesis that inhibition of the low affinity site PDE 4 is associated with the anti-inflammatory actions of this class of compounds, whereas inhibition of the high affinity site is associated with the production of certain side effects, we determined the ability of various PDE 4 inhibitors to block inflammatory cell function both *in vitro* and *in vivo* and the ability of these compounds to produce side effects in *in vitro* and *in vivo* models. To compare the ability of PDE 4 inhibitors to elicit a given therapeutic effect or side effect with their ability to inhibit the low affinity binding site versus their ability to inhibit the high affinity site of PDE 4, we compared the potency of these compounds in the *in vitro* or *in vivo* assays with their potency against the isolated enzyme catalytic activity or the high affinity site by a linear correlation of (r^2) or a rank order correlation (Spearman's Rho). The linear correlation asks whether the potency of a compound at inhibiting either the low affinity site or the high affinity site can be used to predict the ability to elicit a given anti-inflammatory or side effect. The rank order correlation tests whether the rank order potency in producing a given anti-inflammatory or side effect is similar to the rank order potency in inhibiting the low affinity or the high affinity site. Both r^2 and Spearman's Rho were calculated using the STAT View II computer program for the Macintosh.

PDE 4 versus Rolipram high affinity Binding

Example 1 -- Phosphodiesterase and Rolipram Binding Assays

Example 1A

Isolated human monocyte PDE 4 and hrPDE (human recombinant PDE4) was determined to exist primarily in the low affinity form. Hence, the activity of test compounds against the low affinity form of PDE 4 can be assessed using standard assays for PDE 4 catalytic activity employing 1 μM [^{3}H]cAMP as a substrate (Torphy et al., *J. of Biol. Chem.*, Vol. 267, No. 3 pp1798-1804, 1992).

Rat brain high speed supernatants were used as a source of protein. Enantionmers of [^{3}H]-rolipram were prepared to a specific activity of 25.6 Ci/mmol. Standard assay conditions were modified from the published procedure to be identical to the PDE assay conditions, except for the last of the cAMP: 50mM Tris HCl (pH 7.5), 5 mM $MgCl_2$, and 1 nanoM of [^{3}H]-rolipram (Torphy et al., *J. of Biol. Chem.*, Vol. 267, No. 3 pp1798-1804, 1992). The assay was run for 1 hour at 30° C. The reaction was terminated and bound ligand was separated from free ligand using a Brandel cell harvester. Competition for the high affinity binding site was assessed under conditions that were identical to those used for measuring low affinity PDE activity, expect that [^{3}H]-cAMP and [^{3}H]5'-AMP were not present.

Example 1B

Measurement of Phosphodiesterase Activity

PDE activity was assayed using a [^{3}H]cAMP scintillation proximity assay (SPA) or [^{3}H]cGMP SPA enzyme assay as described by the supplier (Amersham Life Sciences). The

reactions were conducted in 96-well plates at room temperature, in 0.1 ml of reaction buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 8.3 mM MgCl2, 1.7 mM EGTA, [^{3}H]cAMP or [^{3}H] cGMP (approximately 2000 dpm/pmol), enzyme and various concentrations of the inhibitors. The assay was allowed to proceed for 1 hr and was terminated by adding 50 µl of SPA yttrium silicate beads in the presence of zinc sulfate. The plates were shaken and allowed to stand at room temperature for 20 min. Radiolabeled product formation was assessed by scintillation spectrometry. Activities of PDE3 and PDE7 were assessed using 0.05 µM [^{3}H]cAMP, whereas PDE4 was assessed using 1 µM [^{3}H]cAMP as a substrate. Activity of PDE1B, PDE1C, PDE2 and PDE5 activities were assessed using 1µM [^{3}H]cGMP as a substrate.

[^{3}H]R-rolipram binding assay

The [^{3}H]R-rolipram binding assay was performed by modification of the method of Schneider and co-workers, see Nicholson, et al., *Trends Pharmacol. Sci.*, Vol. 12, pp.19-27 (1991) and McHale et al., *Mol. Pharmacol.*, Vol. 39, 109-113 (1991). R-rolipram binds to the catalytic site of PDE4 see Torphy et al., *Mol. Pharmacol.*, Vol. 39, pp. 376-384 (1991). Consequently, competition for [^{3}H]R-rolipram binding provides an independent confirmation of the PDE4 inhibitor potencies of unlabeled competitors. The assay was performed at 30°C for 1 hr in 0.5 µl buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$, 0.05% bovine serum albumin, 2 nM [^{3}H]R-rolipram (5.7 x 104 dpm/pmol) and various concentrations of non-radiolabeled inhibitors. The reaction was stopped by the addition of 2.5 ml of ice-cold reaction buffer (without [^{3}H]-R-rolipram) and rapid vacuum filtration (Brandel Cell Harvester) through Whatman GF/B filters that had been soaked in 0.3% polyethylenimine. The filters were washed with an additional 7.5-ml of cold buffer, dried, and counted via liquid scintillation spectrometry.

Formulation Examples

A: Metered Dose Inhalers

Table 1

	Per actuation
Cilomilast	18 mg
Loratadine	12 mg
1,1,1,2-Tetrafluoroethane	to 75.0mg

The micronised active ingredients (eg. for 120 actuations) are weighed into an aluminum can, 1,1,1,2-tetrafluoroethane is then added from a vacuum flask and a metering valve is crimped into place.

B: Dry Powder Inhalers

Table 2

	Per cartridge or blister
Cilomilast	150 micrograms
Loratadine	100 micrograms
Lactose Ph. Eur.	to 12.5mg

The active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs to be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of Glaxo Group Limited).

C Formulations for nasal administration

Table 3

Cilomilast	150mg
Loratadine	100mg
Phenylethyl alcohol	0.25mL
Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591)	1.5mg
Benzalkonium chloride	0.02mg
Hydrochloric acid	to pH 5.5
Purified water	to 100mL.

In a 100µl metered volume dispensed by a Valois VP7 pre-compression pump, approximately 150mcg of cilomilast and 100mcg of loratadine will be delivered.

D. Oral Tablet

Table 5 sets out a tablet formulation which can be used to administer a combination of PDE4 inhibitor and an H_1 receptor antagonist.

Table 5

Composition	Unit Formula (mg/tablet)
Cilomilast	15.0
Loratadine	10.0
Lactose, Monohydrate	93.0
Microcrystalline Cellulose	70.0

Sodium Starch Glycolate	10.0
Magnesium Stearate	2.0
Total weight	200.0mg

Tablet preparation is by conventional means using standard dry-powder mixing and a compression tableting tool.

What is claimed is:

1. A method of prophylaxis, treating, or reducing the duration or frequency of the exacerbations associated with a respiratory disease comprising administering to a patient in need thereof an effective amount of a PDE 4 inhibitor and an H_1-receptor antagonist.
2. The method of claim 1 wherein the PDE4 inhibitor is *cis* [cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate], roflumilast or N-(3,5-dichloropyrid-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide) and the H_1-receptor antagonist is astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, terfenadine or fexofenadine hydrochloride.
3. A composition for the prophylaxis of, treating, or reducing the exacerbations associated with, a pulmonary disease comprising an effective amount of a PDE4 inhibitor, an effective amount of an H_1-receptor antagonist and a pharmaceutically acceptable excipient.
4. The composition of claim 2 wherein the PDE4 inhibitor is *cis* [cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate], roflumilast or N-(3,5-dichloropyrid-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide) and the H_1-receptor antagonist is astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, terfenadine or fexofenadine hydrochloride.
5. The composition of claim 2 or 3 which is an oral tablet.
6. The composition of claim 2 or 3 which is a dry powder for use in a dry powder inhaler.
7. The composition of claim 2 or 3 which is an aqueous preparation for nasal administration.
8. The composition of claim 2 or 3 in which the PDE4 inhibitor and the H1-receptor antagonist is combined with a propellant to form a composition which is delivered using a metered dose inhaler.
9. Use of an effective amount of a PDE4 inhibitor and an effective amount of an H_1-receptor antagonist in the manufacture of a medicament for the prophylaxis, treatment or reduction in duration or frequency of the exacerbations associated with a respiratory disease.
10. Use of an effective amount of a PDE4 inhibitor and an effective amount of an H_1-receptor antagonist in the prophylaxis, treatment or reduction in duration or frequency of the exacerbations associated with a respiratory disease.

INTERNATIONAL SEARCH REPORT

Int[redacted]pplication No
PCT/[redacted]02/02679

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/192 A61K31/4545 A61K31/44 A61K31/4439
A61K31/454 A61K31/451 A61K31/445 A61P11/06 A61P11/08
//(A61K31/4545,31:192)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, PASCAL, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ASHTON M J ET AL: "SELECTIVE TYPE IV PHOSPHODIESTERASE INHIBITORS AS ANTIASTHMATIC AGENTS. THE SYNTHESES AND BIOLOGICAL ACTIVITIES OF 3-(CYCLOPENTYLOXY)-4-METHOXYBENZAMIDES AND ANALOGUES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 11, 1994, pages 1696-1703, XP002015726 ISSN: 0022-2623	1,3,9,10
A	abstract page 1700, right-hand column	2,4-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2002	24/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornich, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BUNDSCHUH D S ET AL: "IN VIVO EFFICACY IN AIRWAY DISEASE MODELS OF ROFLUMILAST, A NOVEL ORALLY ACTIVE PDE4 INHIBITOR" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 297, no. 1, 2001, pages 280-290, XP001024809 ISSN: 0022-3565 abstract page 281, left-hand column page 290, left-hand column ---	1-10
Y	MARX D ET AL: "THE N VIVO ACTIVITY OF AWD 12-281, A POTENT PDE4 INHIBITOR FOR THE TREATMENT OF ALLERGIC ASTHMA" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 103, no. 1, PART 2, January 1999 (1999-01), page S127 XP001098342 ISSN: 0091-6749 the whole document ---	1-10
Y	US 5 990 147 A (ASLANIAN ROBERT G) 23 November 1999 (1999-11-23) column 4, line 10 - line 12 column 4, line 41 - line 67 ---	1-10
Y	WO 99 32125 A (SCHERING CORP ;DANZIG MELVYN R (US); JENSEN PEDER K (US); MEDEIROS) 1 July 1999 (1999-07-01) abstract page 2, line 2 - line 5 page 2, line 30 - line 35 claim 1 -----	1-10

INTERNATIONAL SEARCH REPORT

Application No.
PCT/GB 02/02679

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1, 2 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The subject-matter of present claims 1, 3, 9 and 10 (and the dependent claims 5-8) is defined by means of functional features:

a) PDE 4 inhibitor
b) H1-receptor antagonist

Because of the character of the functional features, it cannot be guaranteed that the performed search is complete.

It cannot be excluded that compounds fulfilling the requirements of the functional features have not been identified as doing so in the prior art.
If such compounds have not been identified in the application either, they have not been covered by the search.

The search has been carried out based on the functional features per se as well as the examples given in the application and the compounds structurally identified by name in claims 2 and 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNAT[redacted]L SEARCH REPORT

Inte[redacted]plication No
PCT/G[redacted]2/02679

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5990147	A	23-11-1999	NONE		
WO 9932125	A	01-07-1999	AU	1907199 A	12-07-1999
			BR	9814417 A	10-10-2000
			CA	2315721 A1	01-07-1999
			CN	1283115 T	07-02-2001
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			HU	0101369 A2	28-03-2002
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			NO	20003288 A	22-08-2000
			PL	341343 A1	09-04-2001
			SK	8972000 A3	12-02-2001
			WO	9932125 A1	01-07-1999
			ZA	9811731 A	21-06-1999